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Combined pharmacophore-guided 3D-QSAR, molecular docking and molecular dynamics studies for evodiamine analogs as DNA topoisomerase I inhibitors

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ABSTRACT

DNA topoisomerase I (TopoI) is a new important anti-cancer drug target. Pharmacophore, 3D-QSAR, molecular docking and molecular dynamics studies were used to reveal structural and chemical features essential for evodiamine and designing/screening novel and potent inhibitors. The best pharmacophore model consists of four hydrophobic interaction sites and three hydrogen bond receptors. 60 evodiamine analogs were used for constructing the best comparative molecular field analysis (CoMFA, $q^2 = 0.729$, $r^2 = 0.985$) and comparative molecular similarity index analysis (CoMSIA, $q^2 = 0.746$, $r^2 = 0.989$) models, the models had high predictive ability, and the contour map was in good agreement with the generated pharmacophore features. Through virtual screening and structure–activity relationship (SAR), we obtained ten(DS1-8, z1-2) well predicted compounds. By molecular docking and molecular dynamics, we found the electrostatic field had the greatest influence on the residues ASN722 and THR718 in the DNA minor groove and the molecular structure should be planarized and appropriate in this region. The hydrogen bond produced by the inhibitor with the residues GLU356 and ARG364 and the hydrophobic interaction with base TGP11, DA113 play an important role in protein stability of the inhibitors. Results provide favorable theoretical foundation for further structural optimization, design, and synthesis of novel DNA TopoI inhibitor.

1. Introduction

DNA Topoisomerase I (TopoI) is an essential nuclear enzyme. DNA topoisomerase I forms the 3′-tyrosine phosphate ester bond and the 5′-hydroxyl through the nucleophilic attack of the phosphate diester bond of one DNA single strand. The cracked single strand rotates around the DNA, unlocks the positive superhelix state, and continues to duplicate DNA. Therefore, TopoI is essential for processes such as DNA duplication and transcription. TopoI is also an important target in research on antitumor drugs [1]. In addition, most of the TopoI inhibitors reported in literature at present are camptothecin (CPT) [2], indenoisoquinolines [3,4]. However, these classes of inhibitors are associated with poor water solubility, high toxicity and complicated structure [5]. Moreover, the two types of CPT-antitumor drugs in the market induce tumor resistance [6,7]. Therefore, obtaining the antitumor drugs through targeted design and restructuring based on the TopoI inhibitors and in combination with computer-assisted technologies can solve the resistance of the single TopoI inhibitor.

Evodiamine is a major bioactive component in the traditional Chinese medicine Tetradium ruticarpum. Evodiamine is a natural indole alkaloid exhibiting no significant toxicity to normal cells [8]. The physical and chemical properties of evodiamine are also safe. At present, there are three clear targets of evodiamine analog, as follows: TRPV1 [9], aromatic receptor, and topoisomerase [10]. These proteins are important drug targets for treatment of inflammation and tumor. In recent years, researchers, such as Dong et al. [10], discovered and reported the action mechanism and combination mode of evodiamine analog in the combination pocket of human TopoI. They proved that the effect of evodiamine and camptothecin are the same. But the role of E-ring in the protein is not clear. Such TopoI inhibitors also in the region of the DNA minor groove pattern are not clear. Evodiamine analog can regulate TopoI–DNA complex. In the DNA replication, DNA and TopoI first form a new reversible cracking compound. DNA polymerase catalyzes DNA to replicate when TopoI catalyzes DNA to unwind.

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When the evodiamine analog derivatives enter into the cells, they exhibit reversible combination with TopoI–DNA to form the ternary complexes in the cells. Evodiamine analog further consolidates the ternary complexes leading to irreversible ternary complex with the increase of evodiamine analog concentration. DNA meets with the ternary complex during replication. The normal DNA replication process stops. Then, the cells are killed. Many experiments have shown that evodiamine exhibits anti-tumor activity [11]. However, the activity is generally low. Evodiamine is an ideal lead compound. Evodiamine is highly safe and harmless to normal cells. Evodiamine possesses broad anti-tumor spectrum that inhibits tumor invasion and metastasis. Evodiamine is active against drug-resistant tumors. Evodiamine structure is also suitable for further transformation.

Quantitative structure–activity relationship (QSAR) is widely used in drug design [12]. The most widely used are 2D-QSAR and 3D-QSAR. 2D-QSAR mainly uses the physical and chemical parameters or structural parameters of the compound as independent variables, and the biological activity is the dependent variable, the structural information of the compounds was studied by theoretical calculation and statistical analysis tools. 3D-QSAR reflects the non-covalent interaction between drug molecules and macromolecules (proteins or nucleic acids), compared with the 2D-QSAR, 3D-QSAR have more explicit physical meaning and can explain more information. Since 1980, 3D-QSAR gradually replaced by the 2D-QSAR position, became one of the main methods for rational drug design. 3D-QSAR mainly conducts quantitative analysis on the relation between the chemical structural information of drugs and its biological activities by virtue of the mathematical model. 3D-QSAR also identifies the quantitative change rule between structure and activity. 3D-QSAR further predicts the structure and activity of the unknown compounds according to such rule. At present, 3D-QSAR has been extensively applied in the research and development of anti-AIDS drugs, antineoplastic drugs, cardiovascular drugs and anti-inflammatory drugs [13-16]. In this paper, five homologous DNA topoisomerase ligands were used to construct pharmacophores in order to better characterize and explain the activity of DNA topoisomerase I inhibitors. Then, the 60 reported evodiamine compounds were aligned in accordance with the pharmacophore features to obtain good CoMFA [17] and CoMSIA [18] models. The model verified the correlation of its electrostatic, steric, hydrophobic, and hydrogen-bond fields with antitumor activity. In addition the structure–activity relationship from the contour maps was well correlated with the pharmacophoric features. Virtual screening technology is used to identify a new structure for the anti-tumor drug treatment and prove that the pharmacophore model is reliable. Molecular docking and molecular dynamics were used to investigate the mode of action of DNA TopoI and inhibitor. All these methods provide important theoretical foundation for the further structural optimization, designing, screening, and synthesizing of the new DNA TopoI inhibitors.

2. Materials and methods

2.1. Compound and activity data

The 60 evodiamine compounds in the current study were derived from the work of Zhang research group [19,20]. The compounds were divided randomly into two groups in accordance with the random and uniform distribution principles, as well as the difference in compound structure. Among the groups, 49 compounds were treated as the training set for model construction, and 11 compounds were treated as the test set for evaluating the reliability and predictive ability of the model. The IC_{50} values for all compounds were translated into pIC_{50} ($pIC_{50} = -\log IC_{50}$) to construct the 3D-QSAR model. Table 1 shows the structures and activity values of these compounds.

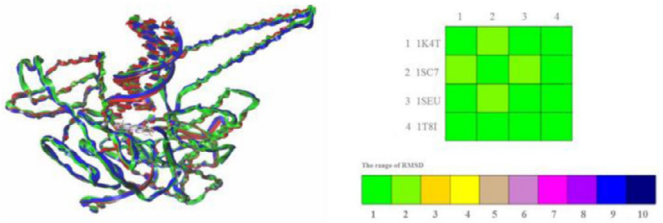

Fig. 1. Protein superimposition and RMSD of the four overlapping proteins.

2.2. Pharmacophore model

Pharmacophore modeling is the most widely used method for identification of essential structural features required for biological activity. The crystal structures of five DNA topoisomerase I inhibitor compounds were obtained from the protein structure database, with details of each protein shown in Table 2. Protein superimposition and RMSD of the five overlapping proteins are shown in Fig. 1. The RMSD value of each of the two composite proteins are all less than 2. The pharmacophore models generated by the ligands in the compounds with the GALAHAD [21] module are of SYBYL2.0 selected. The GALAHAD parameter setting is the combined operation of 45 filial generations and 30 population sizes to generate the five best pharmacophore models shown in Table 3. The value of Pareto is 0 shows none of the model was superior to others. We selected the model with the highest SPECIFICITY value (6.022), since any model with a SPECIFICITY value of over 4 is reliable and can be used [21]. In this way, pharmacophore feature matching enables more structural diversity within the model.

The best pharmacophore model with high specificity was used to screen the ZINC database, which contains a total of 8777 molecules, using UNITY flex research program of Sybyl. Compounds with high QFIT value were further studied by docking them into the putative active site of 1T8I using SurflexDock program. During docking, the ligands were allowed to be flexible, but the receptor remains rigid.

2.3. Molecular structure construction and superposition

Sybyl2.0 software package from Tripos in Windows operating system was adopted in this research. Minimum energy calculation of all structures was performed using the Tripos force field, followed by 10,000 iterations, which was conducted with Powell method [22]. The Gasteiger–Hückel charge was applied during calculation, with the energy convergence criteria being set as 0.005 kcal/(mol·Å), while other parameters were deemed as program defaults. The structure obtained through optimization was placed in the database for model construction.

Molecular superposition is the key step in Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) calculations, and the quality of which directly affects the rationality and the predictive ability of the eventual model. Molecular superposition was conducted on the premise that the ligand molecule analyzed interacted with the biding site of the receptor through the same or similar mode of action. All the molecules in the training set were rigidly aligned to the best pharmacophore model using GALAHAD option of

"Align Molecules to Template Individually". Fig. 2(A) shows the alignment of training compounds. Fig. 2(B) shows the best pharmacophore model aligned to active compound 32, pharmacophore features are color coded (hydrophobes in cyan and acceptor atoms in green).

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